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Nanoparticles in Gastrooncology

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Abstract
Background: Gastrointestinal malignancies have the greatest incidence and cancer-associated death rates worldwide. Routine therapeutic modalities include surgery, chemotherapy and radiation but they often fail to reach the goal of cancer-free survival. ***Summary:*** In the light of this urgent medical need for the treatment of GI tumors, nanotechnology-based approaches, i.e. nanomedicine, promise new therapeutic options. Using nanoparticles instead of classically designed drugs, targeting anticancer agents directly to the tumor site may revolutionize both diagnostic and therapeutic tools thereby facilitating the identification and elimination of malignant cells. Importantly, diagnostic insight and therapeutic effects can be achieved simultaneously through the same nanoparticle. Additionally, a nanoparticle may be loaded with more than one agent, thereby further increasing the value and power of the nanotechnology approach in oncologic therapeutic concepts. Although most insight into mechanisms of nanomedicine has been gained from in vitro and preclinical in vivo models, few clinical trials have been conducted, and nanomedicine-based concepts are already part of standard treatment algorithms. However, despite substantial progress it remains a challenge to design nanoparticles that feature all desirable characteristics at the same time. ***Key Messages:*** This review seeks to provide substantial insight into the current status of nanomedicine-based approaches employed for diagnostic and/or therapeutic purposes in the field of gastrointestinal cancers by highlighting achievements and pointing out unresolved issues that need to be further addressed by future research attempts.

Introduction

Globally, gastrointestinal (GI) tumors are the leading cause for cancer-related death and show the highest incidence. Among those, colorectal cancer, gastric cancer, hepatocellular carcinoma (HCC) and pancreatic cancer are the most frequently observed solid tumors [1]. Even though many attempts to reduce their disease burden have been undertaken, GI tumors are still overall associated with a poor outcome due to both delayed diagnosis in an already incurable state and insufficient therapeutic options in the light of a heterogeneous and so far only partially resolved tumor biology. Accordingly, established treatment regimens consisting of surgery, systemic chemo- and/or immunotherapy and/or local radiotherapeutic measures routinely fail to ultimately cure the majority of patients in advanced tumor stages.

Under the term nanomedicine, nanotechnology-based approaches including designing tumor-targeting nanoparticles are summarized. Nanoparticles represent a very heterogeneous group of particles ranging from 1 to 100 nm in diameter. Their components can be organic or inorganic, and they show different shapes [2]. Currently, mainly gold nanoparticles, magnetic nanoparticles, quantum dots, fluorescence-labeled nanoparticles, graphenes and graphene oxides, and dendrimers and stimulus-responsive polymers are used in research [3]. Nanoparticles can reach their target by an enhanced permeability and retention effect. This effect results from unstructured tumor vessels leaving pores into which nanoparticles can accumulate. Another approach to guide nanoparticles to their target is binding their surface to tumor-specific ligands like antibodies. Nanoparticles as a drug-delivering system are usually characterized by a long circulation time and are protected by liver and kidney metabolism [3]. However, also alternative

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Table 1. Important current and finished clinical trials using nanoparticles

Drug	Nanoparticle type	Status	Disease	Reference
MTL-CEBPA	Lipid	Phase 1	HCC	NCT02716012
DCR-MYC	Lipid	Phase 1/2	HCC	NCT02314052
Irinotecan	Liposome	Phase 1/2	Gastric cancer or gastroesophageal junction adenocarcinoma	NCT03739801
Irinotecan	Liposome	Phase 1/2	Metastatic biliary tract carcinoma, metastatic colorectal carcinoma, metastatic gastroesophageal junction adenocarcinoma, metastatic pancreatic adenocarcinoma	NCT03337087
TKM 080301	Lipid nanoparticle	Phase 1	Secondary liver cancer HCC	NCT01437007 NCT02191878
Paclitaxel	Albumin	FDA/EMA approved	Pancreatic cancer	55, 56
AZD4635	Nanoparticle suspension	Phase 1	Advanced solid malignancies	NCT02740985
Doxorubicin	Doxorubicin docetaxel pluronic block copolymers	Phase 2	Gastroesophageal adenocarcinoma	62

HCC, hepatocellular carcinoma; FDA, Food and Drug Administration; EMA, European Medicines Agency.

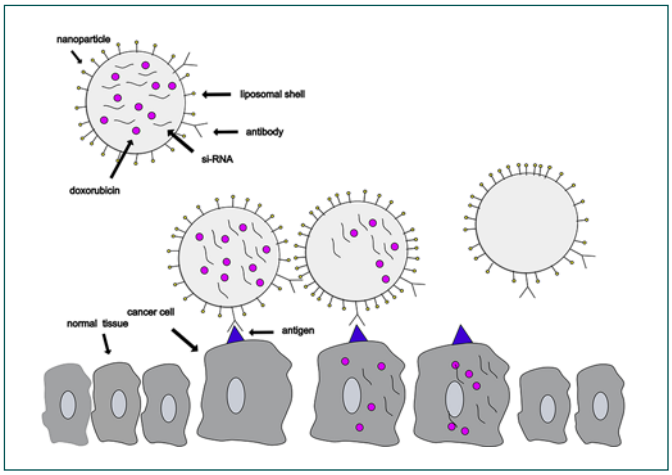

Fig. 1. Example of a nanoparticle working as a nanocarrier: a liposomal nanoparticle is loaded with doxorubicin and siRNA in its core. It is connected to an antibody. The nanoparticle detects the cancer cell via antibody-antigen contact and delivers doxorubicin and siRNA.

application modes have been employed such as direct delivery to the intestinal tumors through an endoscopically guided instillation [4].

Different nanoparticles show distinct characteristics. For example, superparamagnetic nanoparticles can serve as contrast agents in magnetic resonance imaging (MRI). They can also be used as treatment tools when drugs or agents like nucleic acid are bound to them or encapsulated by them (Fig. 1). But nanoparticles can be treatment themselves [2, 5–8]. For example, gold nanoparticles and other nanoparticles are utilized for hyperthermia and photodynamic therapy after irradiation with light in the infrared region [9]. There is a growing body of literature that recognizes the importance of nanomedicine, yet research takes place mainly in vitro and in vivo, but some agents have already been tested in clinical trials (Table 1) or are yet part of standard cure [2, 5–8].

Nanoparticles in Colorectal Cancer

Colorectal cancer (CRC) belongs to the tumors with the highest incidence and mortality in the world. Besides the standard approaches in therapy like surgery, chemotherapy and radiation, great efforts have been made in the field of nanomedicine lately. Evidence from a number of experimental studies has established that nanoparticles represent a feature in treating CRC.

LE-SN38 is a liposomal formulation of SN38, the active metabolite of CPT-11 (irinotecan). This nanoparticle showed greater tumor growth inhibition than CPT-11 in a xenograft model with SCID (severe combined immunodeficiency) mice [10]. Thermodox is used to treat liver metastases, which derive from CRC. It is a liposome that delivers doxorubicin after thermal stimulation, and its use is combined with radiofrequency thermal ablation [8]. Both, LE-SN38 and Thermodox are tested in clinical studies.

CPX-1, a liposome-encapsulated formulation of irinotecan and floxuridine has already completed phase II clin-

ical trials in patients, who had been treated with oxaliplatin or irinotecan previously. Out of 15 patients, 9 showed stable disease, 2 had partial response and only 2 developed progressive disease. Two patients could unfortunately not be evaluated. Six patients showed a progression-free survival of more than 6 months [11].

Yang et al. [12] developed oxaliplatin long-circulating liposomes (pegylated-liposomal oxaliplatin). They could demonstrate that their use was associated with a higher amount of apoptosis in tumors in comparison with free oxaliplatin in vivo using a xenograft mouse model for CRC.

First steps to directly target CRC metastases were performed in an experiment with core/pegylated shell nanoparticles, which delivered DNA for gene therapy. The nanoparticles selectively transfected CRC metastases in vivo, even though only a small fraction of the cells expressed the transgene [13].

The challenge of targeting only the tumor site has been addressed in different experiments.

Of particular concern is A33. The A33 antigen plays a pivotal role in targeting CRC. Its expression in about 95% of all colorectal tumors makes the humanized A33 monoclonal antibody an attractive guide to deliver nanoparticles to the tumor site [14]. The binding to polymer capsules formed by the layer-by-layer method gives the opportunity to deliver drugs and other anticancer agents directly to the tumor [15]. But not only antibodies also peptides can function as a targeting aim.

One study from Gounaris et al. [16] set out to investigate the usefulness of G3-C12 for detecting galectin-3 and G11 to target epidermal growth factor receptor on fluorescently labeled N-(2-hydroxypropyl)methacrylamide copolymers. Furthermore, they connected G11-binding nanoparticles to doxorubicin creating a tumor-specific drug-delivering system.

Besides therapeutical use of nanoparticles, these particles have emerged as powerful platforms for diagnostic approaches. Gounaris et al. [16] were able to identify dysplastic foci within chronically inflamed colons using endoscopic fluorescence imaging in IL-$10^{-/-}$ colitic mice. Through the utilization of lectin-conjugated Fe2O3@Au core@shell nanoparticles, He et al. [17] performed dual-modality imaging to detect colorectal cancer in nude mice in T2-weighted MRI and computer tomography.

Nanoparticles in Gastric Cancer

Determining the impacts of nanomedicine on gastric cancer is important for the future of diagnostics and cancer treatment. Besides that, many research groups do pioneer work combining them, which is named theranostic [18].

Recent research has reported its use in different diagnostic tools such as MRI, fluorescence imaging and endoscopy [7].

Wang et al. [19] used superparamagnetic iron oxide nanoparticles (SPION) for in vitro and in vivo experiments. They coated it with $dSiO_2$ and after labeling with near infrared fluorescence dye and anti-CD146 monoclonal antibody it led to a nanoparticle called 800ZW–SPION@dSiO2–YY146. This nanoparticle was used for in vitro and in vivo imaging. They performed MR/near infrared fluorescence imaging using 800ZW–SPION@dSiO2–YY146 in an MKN45 xenograft tumor model showing its ability to detect gastric cancer by targeting the tumor marker CD146 [19].

Few studies concentrate on nonsupramagnetic nanoparticles. Folic acid-conjugated silica-capped gold nanoclusters designed by Zhou et al. [20] were able to detect FR(+) MGC803 cells in a nude mouse model showing red emitting fluorescence optical property with X-ray absorbance for optical and computed tomography dual-modality imaging of gastric cancer.

Previous research has established the design and implementation of glucose-regulated protein 78 (GRP78)-guided polymeric micelles to diagnose gastric cancer. GRP78 is considered to be a reliable gastric cancer biomarker showing an increased expression level on the cell surface of gastric cancer cells. Cheng et al. [21] coupled the micelles to indium-111 (^{111}In). Tumor imaging with nano single photon emission computed tomography/computed tomography revealed higher radioactive intensity of GRP78-binding protein ^{111}In-labeled micelles in comparison to ^{111}In-labeled micelles without coupled GRP78-binding protein.

Recent studies by Wang et al. [22] included tumor detection in a xenograft tumor model for esophagus cancer in rats using surface-enhanced Raman scattering nanoparticles conjugated to human epidermal growth factor receptor 2 or epidermal growth factor receptor. These nanoparticles were administered orally and endoscopy with multimode fibers for illuminating and detection was performed. Hereby, tumors could not only be detected but the amount of human epidermal growth factor receptor 2 and epidermal growth factor receptor could be quantified.

Theranostic describes the combination of diagnostic and therapy. There are two different manners of it. On the one hand imaging can detect the therapeutic nanoparticle, and on the other hand diagnostic and therapeutic nanoparticles can be administered together [23–26]. Huang et al. [27, 28] designed photosensitizer-conjugated carbon dots called C-dots-Ce6. They combine tumor homing with near infrared fluorescence imaging-guided photodynamic treatment. Additionally, drug agents could be magnetically led to the tumor, and

the magnetic component of the nanoparticle made it visible in MRI.

An innovative technique to deliver drugs using pegylated polycaprolactone nanoparticles containing gelatinase-sensitive peptide was developed by the group of Baorui Liu. Since gelatinases are overexpressed in gastric cancer [29–31], the nanoparticles can target the cancer cells easily and deliver different kinds of agents like chemotherapeutics, small molecules or nucleic acids [32–42].

Besides that, other efforts were undertaken using nanoparticles for treating gastric cancer. SP1049C (Pluronic L61, F127-doxorubicin), a P-glycoprotein targeting micellar formulation of doxorubicin, showed good results in a clinical phase II trial. The objective response rate was 47% (95% CI: 24.4–71) in the evaluable patient population [43].

Nanoparticles in HCC

First steps for the treatment of HCC with nanomedicine were made almost three decades ago. In 1991 Duncan and colleagues [44] developed two different N-(2-hydroxypropyl)methacrylamide copolymers containing doxorubicin and galactosamine, which target hepatocyte galactose receptor, named PK1 and PK2. PK2 targets asialoglycoprotein receptor that is overexpressed in HCC. Patients reported the same side effects with PK2 and unformulated doxorubicin. Asialoglycoprotein receptor expression levels become lower during disease progression suggesting asialoglycoprotein receptor expression as a biomarker for treatment with this agent [6, 44–46].

Xu et al. [47] developed a new nanoparticle carrying doxorubicin, and it shows a low toxicity profile in vivo while being very selective.

A different approach was used by Devulapally et al. [48], when they co-encapsulated gemcitabine and antisense-microRNA-21 in pegylated-poly(lactic) coglycolic acid nanoparticles achieving treatment with two different agents, which was more successful than each agent alone in vitro.

Several studies have investigated the application of small interfering RNAs (siRNA) for HCC treatment [6]. In the context of nanomedicine, Wang et al. [49] designed a nanovector (NP-siRNA-GPC3 antibody) with an iron core and coated with chitosan-polyethylene glycol-grafted polyethylene imine copolymer. This nanovector is conjugated with a monoclonal antibody against human glypican-3 receptor, which shows high expression levels in HCC and transports siRNA. Sun et al. [50] constructed a polyethylene imine-modified liposome, which transports siRNA targeting glypican-3 and sorafenib, a mulltikinase inhibitor, which is a standard drug for HCC treatment with partially serious side effects. There are several other studies going on in vitro and in vivo testing the different characteristic potentials of nanoparticles including the delivery of nucleic acids, drug agents or providing endogenous toxicity. Recent research reported about a thermosensitive liposomal formulation named Thermodox, which forms holes after being heated up to 40–45 °C leading to the release of a loaded drug with promising results in a phase III clinical trial [51]. CEBPA (CCAA/enhancer-binding protein α), a regulator in hepatic function, is downregulated in HCC. Coating activating RNA in a liposomal nanoparticle and administering it in a rodent HCC model reduced tumor burden, so this formula called MTL-CEBPA was further tested in clinical trials [52, 53]. The overexpression of Polo-like kinase 1 in HCC led to a phase I clinical trial using siRNA encapsulated in lipid nanoparticles. Due to limited effects no further studies in HCC are planned [54]. However, this substance is now being investigated for the treatment of liver metastases (NCT01437007).

Nanoparticles in Pancreatic Cancer

Pancreatic cancer belongs to the cancer types in which nanoparticles are already part of standard treatment. It is now well established from a variety of studies that the albumin-bound nanoparticle nab-paclitaxel (abraxane) is part of first-line treatment in unresectable and metastatic disease [55, 56].

Gemcitabine is another standard chemotherapeutic in pancreatic cancer. Patra et al. [57] designed a gold nanoparticle that delivers gemcitabine and used cetuximab (a monoclonal epidermal growth factor antibody) to guide it to the tumor site. In this experiment, tumor inhibition was increased in vitro and in vivo.

A key issue in treating pancreatic cancer is the development of resistance to gemcitabine due to CD47, which provides an antiphagocytosis signal. Therefore, gemcitabine has been coupled to iron oxide magnetic nanoparticles that include an anti-CD47 antibody. This formula inhibited tumor growth in vivo [58]. Hoskins et al. [59] used coupled bisnaphthalimidopropyldiaaminooctane, a novel drug against pancreatic cancer with poor water solubility, to polyallylamine grafted with 5% mole cholesteryl pendant groups. So, the drug is discharged through holes in the shell. In vitro this nanoparticle showed a higher cytotoxic effect on pancreatic cancer cells than gemcitabine.

There are different approaches using metal and metal oxide nanoparticles with antipancreatic cancer activity [5]. For example, cerium oxide nanoparticles sensitize cancer cells to radiation, when administered before treatment while being nontoxic to normal tissue [60]. Pal et al.

[61] designed plectin-1-pancreatic targeting peptide-gold nanoparticles, which deliver gemcitabine to pancreatic cancer. It has a huge advantage due to its selectivity in vivo.

Conclusion

Nanomedicine has the potential to improve diagnostic tools and increase therapeutic options for GI cancers. The heterogeneity of available nanoparticles seems to provide a great advantage, for there are many different options going along with it like binding and encapsulating drugs, different agents and target-directed therapy. Some nanoparticles are already in clinical use. The delivery of one or more anticancer drugs directly to the tumor site and the fact that some nanoparticles can be used for imaging make them very attractive. Published results from in vitro and in vivo research are indeed promising. Yet, some limitations must be taken into account. First, most research on nanoparticles has been performed in vitro and in vivo, while clinical data are rarely available. Hence, the efficacy of individual nanoparticles must be evaluated in clinical studies. In fact, some nanoparticles with promising results in vitro and in vivo failed in clinical tests. Similarly, data on safety and toxicity of distinct nanoparticles are sparse. Another negative aspect considers the costs as well as the complexity of the designing and manufacturing under controlled pharmaceutical production conditions. Still, nanomedicine is an interesting and promising field in medical science. Since it deals with medicine, physics, pharmacology and chemistry there is a huge need for multidisciplinary research.

Disclosure Statement

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Author Contributions

A.J.: writing – original draft; writing – review and editing. M.F.N.: writing – original draft; writing – review and editing.

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